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Two-Year Outcomes of High Bleeding Risk Patients after Polymer-Free Drug-Coated Stents

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ABSTRACT

Background: For patients at high risk for bleeding, a polymer-free metallic stent coated with biolimus-A9 followed by one-month dual antiplatelet therapy was safer and more effective than a bare metal stent at one year.

Objectives: Longer-term follow-up is needed to determine whether these benefits are maintained.

Methods: In a prospective, multi-center, double blind trial, we randomly assigned 2466 high bleeding risk patients to receive a drug coated stent (DCS) or a bare metal stent (BMS) followed by one month dual antiplatelet therapy and 98.1% completed a two-year follow-up. The primary safety end point was a composite of cardiac death, myocardial infarction (MI), or stent thrombosis (ST). The primary efficacy end point was clinically driven target-lesion revascularization.

Results: At 2 years, the primary safety endpoint had occurred in 147 DCS (12.6%) and 180 BMS patients (15.3%) (hazard ratio 0.80; 95% CI, 0.64 to 0.99; p=0.039). Clinically driven target-lesion revascularization occurred for 77 DCS (6.8%) and 136 BMS patients (12.0%) (hazard ratio, 0.54; 95% CI, 0.41 to 0.72; P<0.0001). Major bleeding occurred in 8.9% DCS and 9.2% BMS patients (p=0.95), and a coronary thrombotic event (MI and/or ST) in 8.2% DCS and 10.6% BMS patients (p=0.045). Mortality was 27.1% one year after a major bleed, and 26.3% one year after a thrombotic event. At two years, multivariate correlates of major bleeding were age > 75, anemia, raised plasma creatinine and planned long-term anticoagulation. Correlates of the primary safety endpoint were age anemia, congestive heart failure, multivessel disease, number of stents implanted and use of a BMS rather than a DCS.

Conclusions: The safety and efficacy benefits of DCS over BMS were maintained up to two years in high bleeding risk patients. During that period, overall rates of major bleeding and coronary thrombotic events were no different and associated with a substantial and comparable mortality risk.

Clinical Trial: NCT01623180.

Keywords: drug-coated stent, DAPT, bleeding, thrombosis, bare-metal stent

Abbreviations:

BARC = Bleeding Academic Research Consortium
BMS = Bare metal stents
DAPT = Dual antiplatelet therapy
DCS = Drug-coated stents
DES = Drug-eluting stents
HBR = High bleeding risk
PCI = Percutaneous coronary intervention

Introduction

Patients at high bleeding risk (HBR) who require percutaneous coronary intervention (PCI) are a challenging group who need careful evaluation of both their thrombotic and bleeding risks when selecting a stent and deciding on duration and intensity of antithrombotic management (1,2). Little evidence exists to aid such decisions, since HBR patients are mostly excluded from clinical trials of antithrombotics and PCI (3-6). Until recently, the perceived need for a very short course of dual antiplatelet treatment (DAPT) often led operators to prefer a bare metal stent (BMS) to a drug eluting stent (DES) for such patients (7,8).

The Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk (LEADERS FREE) trial recently showed that, together with a one month DAPT course, a polymer-free metallic drug coated stent (DCS) was both safer and more effective than a BMS for patients at high risk of bleeding followed for one year (1). This DCS (BioFreedom, Biosensors Interventional Technologies Pte, Ltd., Singapore) transfers biolimus A9, a highly lipophilic sirolimus analog, into the vessel wall over a one month period (9). This is in contrast to currently available polymer-coated Drug-Eluting Stents (DES), which generally release drug over a period of several months.

Limited encouraging five-year data are available from the first-in-man evaluation of this DCS for 60 selected patients treated with 6-12 months DAPT (10). For HBR patients with one-month DAPT treatment, further evidence is needed to assess whether the first year benefits of DCS over BMS are maintained in the long term. Also, because of the unique features of the LEADERS FREE design (unusual patient population, very short DAPT) together with the observed high rate of major bleeding in both arms after one year,[1] it appeared important to

evaluate the balance of the two-year risks and the baseline and procedure correlates of the primary safety endpoint and of major bleeding events.

Methods

Patients

Patient selection and study design of the LEADERS FREE trial have been described previously (1,11). Inclusion required a clinical indication for PCI together with one or more HBR criteria: most frequently age 75 or above, planned prolonged oral anticoagulation, renal insufficiency, planned major surgery, anemia or recent transfusion and cancer. Such patients were potential candidates for a BMS instead of a DES, owing to their perceived need for only one month DAPT.

Study Device and Procedure

The BioFreedom polymer-free biolimus A9 coated stent, the control Gazelle bare-metal stent (Biosensors Europe and Biosensors Interventional Technologies) and the PCI procedure have been described previously (1,11). Importantly, a double-blind design was used. All patients were to receive DAPT including both aspirin (75 to 250 mg once daily) and a P_2Y_{12} inhibitor (with clopidogrel preferred) for 30 days followed by a single antiplatelet agent thereafter (aspirin preferred). Patients requiring a vitamin K antagonist could be treated either by triple therapy or a vitamin K antagonist plus clopidogrel only during the first 30 days. Patients had follow-up visits at 30 and 365 days, and were contacted either on site or by telephone at 60, 120 and 730 days. Ischemia testing and angiographic evaluation during follow-up was left to the investigator's discretion.

Study Design and Oversight

A total of 2466 patients from 68 sites were randomized to receive either the BioFreedom DCS or the Gazelle BMS. The study was sponsored by Biosensors Europe (Morges, Switzerland), and conducted by the Cardiovascular European Research Center (CERC; Massy, France), an independent research organization paid by the sponsor. The respective roles of the Executive Committee, the Sponsor, CERC and authors have remained unchanged (1). The first author, statisticians (JG, SC) and Executive Committee had unrestricted access to the data and prepared all drafts of the manuscript; they attest to the completeness and accuracy of all data and to the adherence to study protocol. The Ethics Committee at each site approved the trial, and written informed consent was obtained from all patients.

Study End Points

The primary safety endpoint was the cumulative incidence of a composite of cardiac death, myocardial infarction, or definite or probable stent thrombosis. The primary efficacy endpoint was the incidence of clinically driven target-lesion revascularization. Pre-specified secondary end points included all-cause and cardiac mortality, bleeding (Bleeding Academic Research Consortium (BARC) definitions) (12), myocardial infarction (3rd Universal definition) (13), stent thrombosis (Academic Research Consortium (ARC) definitions) (14), and types of coronary revascularization. A clinical events committee adjudicated all components of the primary end points and all bleeding events, according to pre-defined criteria (1,11).

Statistical Analysis

All results are based on a modified intention to treat analysis after exclusion of 34 patients who had no suitable lesion for PCI (1). Continuous variables are presented as means, categorical data as counts and percentages. Time-to-event analyses were performed using Kaplan–Meier plots, log-rank tests and proportional-hazard models to estimate hazard ratios and

their 95% confidence intervals. Proportional hazard assumptions were checked using Schoenfeld residuals. Patients were censored at death, withdrawal from study, scheduled end of study, or 730 days post-randomization, whichever occurred first. We performed sensitivity analyses using the Fine and Gray method to estimate cumulative incidence of events whilst adjusting for the competing risk of mortality (15).

For major bleeding we used the BARC 3, 4 or 5 bleeding definition. To explore covariates associated with major bleeding and the primary safety endpoint, we performed multivariate analyses investigating the potential influence of 32 baseline and procedural variables (Online Table 1) by means of proportional hazard models. We selected a final model for each outcome by using forward stepwise variable selection on data with complete information on all covariates and an inclusion criterion of $p<0.01$. Based on the trial results, we forced inclusion of BMS stent in the model for the primary safety endpoint. We used multiple imputations with chained equations to impute missing data on covariates when calculating hazard ratios. We used 10 imputed datasets and combined estimates and standard errors across studies using Rubin's rules (16). To calculate the hazard ratios for death following a thrombotic or major bleeding event, follow-up of each patient was divided into time spent before and after a major bleeding or thrombotic event. The association between these events and subsequent mortality was entered into a Cox-proportional hazards model as a time-updated categorical variable that enters the model on the day of the event (Online Appendix E). HRs therefore compare the hazard of death after an event to the hazard before an event (which includes the hazard in patients who do not have an event during follow up). We further broke each patient's follow-up after a thrombotic or major bleeding event into three time intervals (0-7, 8-30, and 31-365 days), based upon similar analyses performed in other studies (17).

Hazard ratios for death were adjusted for correlates of thrombotic or major bleeding events. Analyses were performed with Stata Software, version 14.1 (StataCorp) and SAS 9.3 and all p-values were calculated using 2-sided hypothesis tests.

Results

Patients

Of the 2432 patients who underwent PCI, 2386 (98.1%) were followed until death or 730 days (Online Figure 2). Only 9 patients in the DCS arm and 3 in the BMS arm were lost to follow-up before 2 years. Patients were included based on pre-defined criteria of an increased bleeding risk, mainly age ≥75 (64.3%), prolonged oral anticoagulation (36.1%), renal failure (19.1%), planned major surgery (16.4%), hemoglobin <11g/l or recent transfusion (15.6%) and cancer in the previous 3 years (9.8%). The DCS and BMS groups were well matched with regard to baseline characteristics (Online Table 3).

At 730 days, 78.8% of patients in the DCS group and 76.8% in the BMS group were receiving single antiplatelet therapy, 5.3% and 7.6% respectively had dual antiplatelet therapy, 15.8% and 15.6% respectively were taking no antiplatelet drug and 37.7% and 38.0% respectively were taking oral anticoagulants. Details regarding antithrombotic treatment are given in Online Table 4.

Primary Outcomes at 2 Years

We previously reported outcomes using a 390 day time-point (1). In order to facilitate comparisons between the first and second follow-up year, time-points of 365 and 730 days were used for 1 and 2 years in the present analysis. Between 1 and 2 years, there were 53 new occurrences of a primary safety endpoint in 37 DCS patients and 44 in 29 BMS patients. The primary safety outcomes at 2 years occurred more frequently in the BMS than in the DCS group

(15.3% vs.12.6%, hazard ratio, 0.80; 95% confidence interval [CI], 0.64 to 0.99, P=0.039) (**Table 1, Figure 1 and Central Illustration**).

Between 1 and 2 years, there were 24 new clinically driven target-lesion revascularizations (primary efficacy end point) in 20 patients of the DCS group and 43 in 29 patients of the BMS group. Clinically driven target-lesion revascularization was required at least once in 6.8% of DCS and 12.0% of BMS patients at 2 years (hazard ratio, 0.54; 95% CI, 0.41 to 0.72, P<0.0001) (**Table 1, Figure 1 and Central Illustration**).

Other Clinical Outcomes

Other clinical outcomes are summarized in **Table 1**. There were no significant differences in mortality between the DCS and BMS groups in either all-cause (13.1% vs. 13.8%, hazard ratio 0.94; 95% CI, 0.75 to 1.17, P=0.57) or cardiac mortality (6.6% vs. 6.9%, hazard ratio 0.94; 95% CI, 0.69 to 1.28, P=0.69) (**Table 1**). Between 1 and 2 years follow-up, 48 myocardial infarctions occurred (25 in 20 patients of the DCS group, and 23 in 14 patients of the BMS group) and two very late definite or probable stent thromboses (1 in the DCS group and 1 in the BMS group).

The incidence of coronary thrombotic events from randomization to 2 years (defined as any myocardial infarction and/or definite or probable stent thrombosis) was significantly lower with DCS than with BMS (8.2% vs. 10.6%, p=0.045) (**Table 1**). Major bleeding over 2 years occurred at a similar rate in both DCS and BMS groups (8.9% vs. 9.2% p=0.95) (**Central Illustration**). Pre-specified subgroup comparisons for the primary efficacy and safety end points are shown in Online Figure 3. These analyses show a consistent treatment effect across most subgroups. However, interaction testing suggested heterogeneity of treatment effect with regard to the primary safety end point according to whether or not the patient presented with an acute

coronary syndrome, and with regard to the primary efficacy end point in patients with a CRUSADE score greater than 35. Both these subgroups had already been identified at the one-year follow-up. (1).

We identified eight baseline and procedural characteristics correlated with major bleeding and primary safety endpoint events at two years: four were related to the safety endpoint only (congestive heart failure, multivessel disease, number of stents and stent type), two to bleeding events only (planned oral anticoagulation and raised plasma creatinine) and two to both (age >75 and low hemoglobin) (**Table 2**). Of note, use of a BMS had a 33% relative increase in the hazard for safety endpoint events (p=0.04) compared to DCS after covariate adjustment.

The risks of all-cause death one year after a major bleed and one year after a coronary thrombotic event were 27.1% and 26.3% respectively (**Figure 2A**). Both show a similar pattern with very marked excess mortality risk within the first week after such events, especially for coronary thrombotic events, which then attenuates over time (**Figure 2B**). A major bleed remains associated with a significant excess mortality risk during 31-365 days after the event (adjusted hazard ratio 2.54, p<0.001). These mortality patterns were no different for both DCS and BMS groups, though the former has a reduced risk of a coronary thrombotic event (**Table 1**).

Discussion

For HBR patients receiving a one-month course of DAPT, two-year follow up in the LEADERS FREE trial demonstrates, for both efficacy and safety, the sustained superiority of the BioFreedom polymer free biolimus A9-coated stent (DCS) compared to a similar bare-metal stent (BMS). In this patient population, both the risks of major bleeding and of a composite of cardiac death, myocardial infarction or stent thrombosis were high. Both type of events were associated with several baseline and procedure characteristics, and when two of the components

of the primary safety endpoint (MI and/or ST) were analyzed for their associated post-event one year all-cause mortality, this was high: 26.3% and comparable to that observed after major bleeding (27.1%).

Encouragingly for the DCS, no "catch-up" of target lesion revascularization was observed beyond one year. This is in keeping with studies of a polymer-free stent as well as a rapid-elution permanent polymer DES (18,19) and different from what has been seen with first generation DES (20). It is plausible that biolimus A9 is particularly well suited to rapid delivery into the vessel wall because of its marked lipophilicity (9). The low incidence of very late stent thrombosis in both trial arms (<0.1%) suggests that absence of any polymer on the DCS may contribute to its long-term safety despite the very short DAPT, and compares favorably with stent thrombosis rates for polymer-coated DES, especially in this high risk population (21-26).

These data confirm the good long-term results of DCS observed in a previous study (10). However, HBR patients continue to suffer a high incidence of adverse events beyond the first year, most likely due to advanced age, major co-morbidities, and possibly because of only partial revascularization in some patients (multivessel disease was reported in 62% of patients, but multivessel index revascularization was done in only 22%) (1). Two-year mortality was 13.1% for DCS vs. 13.8% for BMS patients. This is higher than observed in all-comer trials, and again points to the impact of comorbid conditions (23,26-29).

The ZEUS trial randomized 1606 patients considered uncertain DES candidates to either a first generation rapid-elution zotarolimus DES with a biocompatible permanent polymer or a thin-strut BMS (30). Among these patients, 52% had a high bleeding risk, and their median DAPT duration was 30 days. The overall trial found better safety and efficacy for the DES, even more pronounced for HBR patients with substantial reductions in myocardial infarction and

target vessel revascularization and a stent thrombosis rate of 2.6% vs. 6.2% for DES and BMS respectively (2,30). Two other randomized trials evaluated this rapid-elution Zotarolimus-eluting DES in low bleeding risk patients, and concluded that a 3 month course of DAPT was as safe and effective as a prolonged course of DAPT, but both were somewhat underpowered (5,6). The larger DAPT trial enrolled 9961 low to medium bleeding risk patients after implantation of several slow-eluting DES and an uneventful first 12 months period, and evaluated prolonged DAPT. Rates of myocardial infarction and stent thrombosis were significantly lower with 30 than with 12 months DAPT, but at the cost of an increase in bleeding (31).

The recent NORSTENT trial randomized 9013 patients to either a contemporary DES or a thin-strut BMS, and found that with a 9 month DAPT course in both arms and after a 6 year follow-up, both stent types were equivalent for safety (cardiac death or MI), while DES were superior in terms of need for repeat revascularisation and a lower rate of stent thrombosis (32). Since both the DAPT duration and the patients risk profiles were very different from those of LEADERS FREE, we believe that both trials complement rather than contradict each other. BMS design is unlikely to be a major factor, since the thin strut BMS used in NORSTENT were very similar to those used in ZEUS, where active stents were also both safer and more effective than BMS in HBR patients treated with a short course of DAPT (2,30).

Interest in shortening DAPT when needed is now considerable, and there are at least 9 randomized trials currently planned or ongoing to evaluate DAPT regimens of 3 months or less after coronary stenting. Some use stents with rapid drug transfer to the vessel wall, a logical feature when very short DAPT appears desirable, while others use stents coated with either a permanent or biodegradable polymer that delivers the anti-proliferative drug over several months. Whether such strategies are safe remains to be demonstrated (33).

One important finding in our trial is that both bleeding and coronary thrombotic event rates (MI and/or ST) are high and similar in HBR patients. While this balance has already been described for all-comer patients (34), both types of events are clearly more frequent in HBR patients. In the present trial, 8.2% of patients suffered a coronary thrombotic event (MI and/or ST) and 8.9% % a major bleeding event at 2 years in the DCS group, while these events occurred in 10.6% for thrombotic and 9.2% for bleeding events in the BMS group. In the PARIS registry that analyzed 4190 patients after coronary stenting, the majority of whom were maintained on DAPT for at least a year, coronary thrombotic events occurred in 3.8% and major BARC bleeding (BARC 3 or 5) in 3.3%. (34,37). This difference is again most probably due to the more advanced age and greater co-morbidity of HBR patients, compared to an "all-comer" population. Of interest is the fact that the ratio of thrombotic to bleeding events at two years was very similar in both trials (0.92 for the DCS arm, 1.15 for the BMS arm in LEADERS FREE and 1.15 in PARIS).

The risk of ensuing mortality is also high, especially soon after the event. Of note is the persistently high excess mortality out to one year after a major bleed. These findings are similar to those of ACUITY (17), a trial focused on patients presenting with acute coronary syndrome, but the adjusted hazard ratios for mortality associated with major bleeding and thrombotic events were markedly higher in LEADERS FREE, again suggesting that such events are of greater consequence for HBR than for younger patients with less comorbidity. The trade-off for any change in anti-thrombotic management may be finely balanced: a longer DAPT course might decrease thrombotic complications, but, most likely at the price of an increased risk of major bleeding (35,36). LEADERS FREE was designed to compare a new stent to a BMS using the

accepted standard of one month DAPT in HBR patients, but the optimal duration of DAPT still remains to be determined in this high-risk population.

Among characteristics associated with either bleeding or the primary safety endpoint (**Table 2**), anemia, like age, was related to both. This stresses the limitations of using certain correlates to assess either bleeding or thrombotic risks in isolation when deciding about the intensity and duration of DAPT. As previously reported, anemia is a powerful prognostic indicator after PCI, more so for bleeding than for thrombosis in our series, and has historically received insufficient attention (38-40). For avoidance of bleeding, the need for long-term oral anticoagulation should always be carefully reassessed after PCI (40). Renal insufficiency was correlated only with bleeding in our series, while it has also been reported as a predictor of thrombotic complications by others (34,37). It could either be that its thrombotic risk is of comparative lesser importance for HBR patients who by definition often have other co-morbid conditions, or that patients with the most severe renal dysfunction are already captured by their associated anemia.

Two study limitations should be acknowledged. First, results are not directly applicable to non-HBR patient who are likely to tolerate longer courses of DAPT. For non-HBR patients, a 6-12 months course, perhaps longer, is associated with benefit (7,8,31) and a minimum of 12 months remains the Guideline when such patients present with ACS (7,40). Second, our results cannot be generalized to other DES or DCS with different drugs or slower elution kinetics. Further evidence is needed, and those trials are currently underway.

In summary, the safety and efficacy benefits of a polymer-free biolimus A9-eluting stent vs. a bare metal stent together with a short one-month DAPT course were maintained during two years follow-up. The persistently high incidence of both bleeding and coronary thrombotic

events in HBR patients needs wider recognition, and deserves full attention in future trials of antithrombotic therapy.

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Figure Legends

Central Illustration. High Bleeding Risk Patients after Polymer-Free Drug-Coated Stents: Primary safety endpoint, primary efficacy endpoint, major bleeding, and individual components of the primary safety endpoint. The Kaplan-Meier time-to-event curves show the cumulative percentage of patients with the primary safety end point (a composite of cardiac death, myocardial infarction, or stent thrombosis) (Panel A), the primary efficacy end point (clinically driven target-lesion revascularization) (Panel B), major bleeding (Panel C), and the three components of the safety endpoint (PANELS D, E, and F).

Figure 1: Landmark analysis at one year for the primary safety and primary efficacy endpoints. The Kaplan Meier time-to-event curves show the cumulative percentage of patients who reached the primary safety endpoint (left panel) and the primary efficacy endpoint (right panel) for the first time between 365 and 730 days.

Figure 2. One-year mortality following a major bleed[+] or a coronary thrombotic event.*Kaplan Meier time-to-event curves show the cumulative percentage of patients who died within one year following a major bleed or a thrombotic event* throughout the 2 year study period.

Table 1. Clinical Outcomes at 1 Year and 2 Years with a Drug-Coated or Bare-Metal Stent

Outcome	1 Year			2 Years		
	DCS (N=1221)	BMS (N=1211)	p	DCS (N=1221)	BMS (N=1211)	p
Primary safety end point: cardiac death, MI, or stent thrombosis	110 (9.2)	151 (12.7)	0.006	147 (12.6)	180 (15.3)	0.039
Primary efficacy end point: clinically driven TLR	57 (4.9)	107 (9.3)	<0.001	77 (6.8)	136 (12.0)	<0.0001
Death						
From any cause	91 (7.5)	105 (8.7)	0.27	156 (13.1)	164 (13.8)	0.57
From cardiac causes	49 (4.1)	61 (5.1)	0.23	76 (6.6)	80 (6.9)	0.69
MI‡						
Any	70 (5.9)	103 (8.7)	0.008	90 (7.4)	117 (10.1)	0.04
Q-wave infarction	6 (0.5)	7 (0.6)	0.77	6 (0.5)	10 (0.9)	0.31
Non-Q-wave infarction	55 (4.7)	78 (6.7)	0.04	67 (5.8)	86 (7.4)	0.09
Undetermined type	10 (0.8)	26 (2.2)	0.007	18 (1.6)	31 (2.7)	0.06
Stent thrombosis‡						
Definite or probable	24 (2.0)	26 (2.2)	0.75	25 (2.1)	27 (2.3)	0.76
Definite	16 (1.3)	17 (1.4)	0.84	17 (1.4)	17 (1.4)	0.98
Probable	8 (0.7)	9 (0.8)	0.80	8 (0.7)	10 (0.9)	0.63
Possible	25 (2.2)	26 (2.2)	0.85	36 (3.2)	35 (3.1)	0.95
Early definite or probable (acute + sub-acute)	12 (1.0)	15 (1.2)	0.55	-	-	-
Late definite or probable	13 (1.1)	11 (1.0)	0.70	-	-	-
Very late definite or probable	-	-	-	1(0.1)	1 (0.1)	0.99
Coronary thrombotic event*‡	76 (6.4)	109 (9.3)	0.01	96 (8.2)	123 (10.6)	0.045
Bleeding‡§						
BARC 1-5	213 (17.9)	225 (19.1)	0.50	258 (22.0)	255 (22.3)	0.89
BARC 2-5	165 (13.9)	173 (14.8)	0.61	204(17.4)	206 (17.9)	0.83
BARC 3-5	85 (7.2)	85 (7.3)	0.96	105 (8.9)	105 (9.2)	0.95
Revascularization						
Any TVR	65 (5.6)	119 (10.3)	<0.001	91 (8.1)	151 (13.3)	<0.0001
TVR by CABG	4 (0.3)	11 (1.0)	0.07	6 (0.5)	12 (1.1)	0.14
Any revascularization	94 (8.1)	134 (11.6)	0.003	129 (11.4)	180 (15.9)	0.001

Percentages are Kaplan–Meier estimates at 365 (1 year) and 730 days (2 years).

* Any myocardial infarction and/or definite or probable stent thrombosis

‡ Subcategories of myocardial infarction, stent thrombosis, or bleeding are not mutually exclusive, because patients could have more than one subtype of these events during follow-up.

§Bleeding was defined according to the Bleeding Academic Research Consortium (BARC) definitions. BARC type 0 indicates no bleeding, and BARC type 5 indicates fatal bleeding.[11]

BMS: bare metal stent; CABG: coronary artery bypass grafting; DCS: drug coated stent; MI: myocardial infarction; TLR: target-lesion revascularization; TVR: target-vessel revascularization

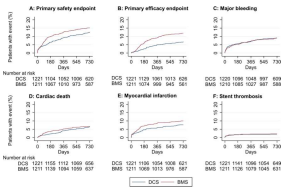
Table 2: Multivariate correlates of primary safety endpoint*and major bleeding[+]

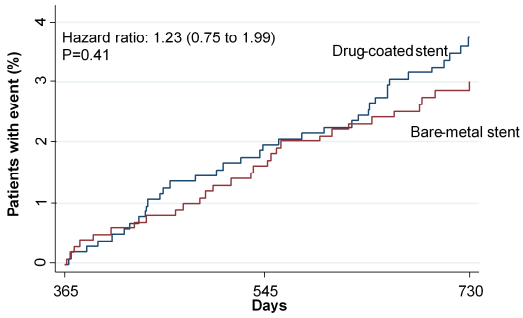
	Hazard ratio	P
Primary safety endpoint		
Age >75 years	1.56 (1.23 to 1.97)	<0.001
Hemoglobin (per 1 mmol/l < 9)	1.32 (1.19 to 1.46)	<0.001
Congestive heart failure at baseline	1.61 (1.23 to 2.11)	0.001
Multivessel disease at baseline**	1.66 (1.27 to 2.18)	<0.001
Number of stents implanted (per additional stent)	1.13 (1.04 to 1.23)	0.005
Bare metal stent	1.28 (1.03 to 1.59)	0.027
Major bleeding event		
Age >75 years	1.52 (1.13 to 2.06)	0.006
Hemoglobin (per 1 mmol/l < 9)	1.73 (1.52 to 1.96)	<0.001
Serum creatinine >150 umol/l	1.58 (1.10 to 2.27)	0.012
Planned OAC use post-PCI	2.01 (1.51 to 2.68)	<0.001

[*] Primary safety endpoint: composite of cardiac death, myocardial infarction and definite/probable stent thrombosis
[+] BARC 3-5 (Bleeding Academic Research Consortium) bleeding
[**] Multivessel vessel disease includes patients with site-reported two or three vessel and/or left main disease.
OAC: Oral anticoagulants; PCI: percutaneous coronary intervention

Table 3: 1-year mortality following a major bleed or coronary thrombotic event

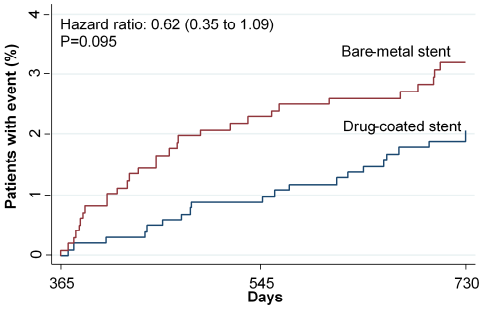
	Patients with event	Deaths	Person-time at risk (years)	Rate (per person-year at risk)	Adjusted hazard ratio vs no event (95% CI)
First year after event					
Thrombotic event					
No event or before event	2432	256	4137.3	0.06	1.00 (reference)
0-365 days	219	64	257.3	0.25	4.43 (3.24 to 6.04)
Major bleeding					
No event or before event	2432	255	4153.5	0.06	1.00 (reference)
0-365 days	210	65	241.1	0.27	3.43 (2.49 to 4.74)
Time since event					
Thrombotic event					
No event or before event	2432	256	4137.3	0.06	1.00 (reference)
0-7 days	219	24	3.9	6.22	77.96 (49.29 to 123.30)
8-30 days	195	11	11.8	0.93	11.51 (6.19 to 21.40)
31-365 days	183	29	241.6	0.12	1.53 (0.93 to 2.53)
Major bleeding					
No event or before event	2432	255	4153.5	0.06	1.00 (reference)
0-7 days	210	16	3.8	4.2	36.11 (20.82 to 62.64)
8-30 days	192	3	11.9	0.25	2.41 (0.76 to 7.65)
31-365 days	186	46	225.4	0.2	2.36 (1.60 to 3.48)





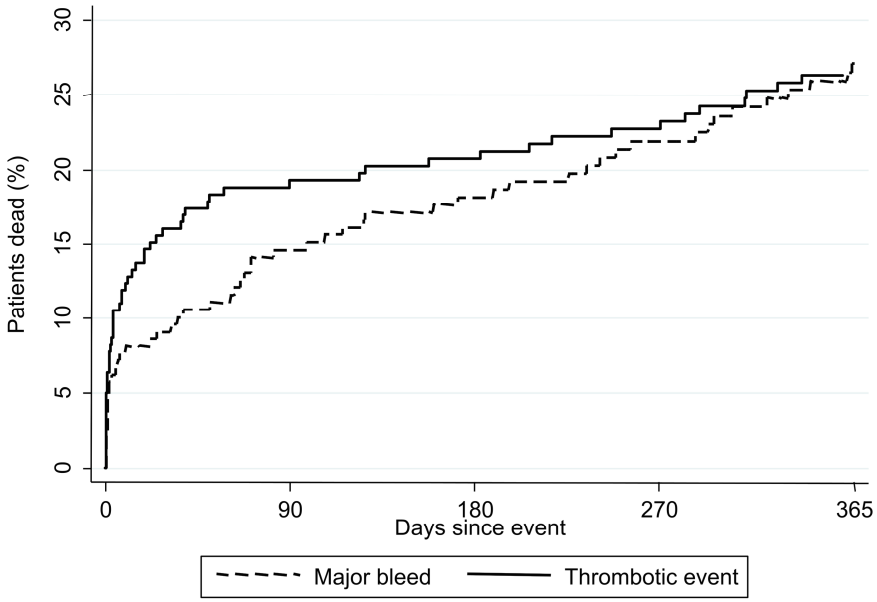
No. at risk

Drug-coated stent	1052	1006	620
Bare-metal stent	1010	973	587



No. at risk

Drug-coated stent	1061	1013	626
Bare-metal stent	999	945	561



SUPPLEMENTARY APPENDIX

Table of contents

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B: Inclusion and exclusion criteria

Inclusion criteria:

Any indication for PCI in patients presenting as stable angina, silent ischemia, ACS (STEMI and non-STEMI), with native or non-native, de novo or in-stent restenosis target lesions, deemed at high risk for bleeding and candidates for 1 month DAPT, satisfying at least one on the following criteria:

1. Adjunctive oral anticoagulation treatment planned to continue after PCI
2. Age ≥ 75 years old
3. Baseline Hemoglobin <11 g/dl (or anemia requiring transfusion during the 4 weeks prior to randomization)
4. Any prior intra-cerebral bleed
5. Any stroke in the last 12 months
6. Hospital admission for bleeding during the prior 12 months
7. Non skin cancer diagnosed or treated < 3 years
8. Planned daily NSAID (other than aspirin) or steroids for >30 days after PCI
9. Planned surgery that would require interruption of DAPT (within next 12 months)
10. Renal failure defined as calculated creatinine clearance <40 ml/min
11. Thrombocytopenia (PLT <100,000/mm3)
12. Severe chronic liver disease defined as patients who have developed any of the following: variceal hemorrhage, ascites, hepatic encephalopathy or jaundice
13. Expected non-compliance to prolonged DAPT for other medical reasons

Exclusion criteria:

1. Pregnant and breastfeeding women
2. Patients expected not to comply with 1 month DAPT
3. Patients requiring a planned staged PCI procedure more than one week after the index procedure
4. Procedure planned to require non-study stents, or stand-alone POBA or stand-alone atherectomy

5. Active bleeding at the time of inclusion

6. Reference vessel diameter <2.25 - >4.0mm

7. Cardiogenic shock

8. Compliance with long-term single anti-platelet therapy unlikely

9. Known hypersensitivity or contraindication to aspirin, clopidogrel (or prasugrel, or ticagrelor if applicable), stainless steel, zinc, umirolimus (also known as biolimus A9) or a sensitivity to contrast media, which cannot be adequately pre-medicated

10. PCI during the previous 12 months for a lesion other than the target lesion of the index procedure

11. Participation in another clinical trial (up to 12 months after index procedure)

12. Patients with a life expectancy of < 1 year

13. Patients under judicial protection, tutorship or curatorship (for France only)

C: Study devices

The BioFreedom drug coated stent (DCS) Coronary Stent Delivery System is comprised of three components including 1) a 316 L stainless steel bare metal stent platform which has been modified with a proprietary surface treatment resulting in a selectively micro-structured, abluminal surface. The selectively micro-structured surface allows 2) the drug, umirolimus [also known as biolimus A9], to adhere to the abluminal surface of the stent without the use of a polymer or binder. The drug-coated stent is crimped onto 3) a delivery system which includes a high pressure, semi-compliant balloon incorporated onto the distal tip of a rapid exchange delivery catheter system. The delivery system has two radiopaque markers inside the balloon, which fluoroscopically mark the ends of the stent to facilitate proper stent placement.

Umirolimus [biolimus A9] is the therapeutic agent used in the BioFreedom DCS. It is a proprietary semi-synthetic sirolimus derivative, highly lipophilic, rapidly absorbed in tissues, and able to reversibly inhibit growth factor-stimulated cell proliferation. Current data suggest that umirolimus, on a molecular level, forms a complex with the cytoplasmic proteins that inhibit the cell cycle between the G0 and G1 phase. The result is an interruption of the cascade governing cell metabolism, growth, and proliferation. For this trial, the BioFreedom DCS was available in six stent diameters (2.25 – 4.0 mm), seven lengths (8-28mm) and one drug dosage (15.6 µg/mm).

The control Gazelle bare metal stent (BMS) consists of a very similar stainless steel platform (the connecting struts are straight instead of curved, a difference not visible to the naked eye), but without the micro-structured abluminal surface or the drug, crimped onto the same balloon delivery system. Both devices were packaged in a numbered but identical non-branded generic fashion, thus allowing for a full double-blind design. Information regarding both the BioFreedom DCS and Gazelle BMS were provided in the Instructions for Use for the Leaders Free study.

D: Endpoint definitions

The primary safety endpoint (non-inferiority and superiority hypotheses) was the cumulative incidence of a composite of cardiac death, myocardial infarction (MI), and definite or probable stent thrombosis at 1 year.

The primary efficacy endpoint (superiority hypothesis) was the incidence of clinically driven TLR at 1 year.

Cardiac death was defined as death due to any of the following:

Acute myocardial infarction.

Cardiac perforation/pericardial tamponade.

Arrhythmia or conduction abnormality.

Stroke within 30 days of the procedure or stroke suspected of being related to the procedure.

Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery.

Any death in which a cardiac cause cannot be excluded.

Myocardial infarction was defined according to the third universal definition:

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

1) Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

- Symptoms of ischemia.
- New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
- Development of pathological Q waves in the ECG.

- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Identification of an intracoronary thrombus by angiography or autopsy.

2) Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

3) Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

4) Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.

5) Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Types of myocardial infarction

Type 1: Spontaneous myocardial infarction

Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary

arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

Type 2: Secondary myocardial infarction

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3: Myocardial infarction related to sudden cardiac death

Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI).

Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Type 4b: Myocardial infarction related to stent thrombosis

Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

Type 4c : Myocardial infarction related to in-stent restenosis

Type 5: Myocardial infarction related to coronary artery bypass graft surgery (CABG)

Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Stent thrombosis was defined according to the Academic Research Consortium (ARC).

Acute stent thrombosis	0 – 24 hours post stent implantation
Sub-acute stent thrombosis	> 24 hours – 30 days post stent implantation
Late stent thrombosis	> 30 days – 1 year post stent implantation
Very late stent thrombosis	> 1 year post stent implantation

Definite stent thrombosis is considered to have occurred by either angiographic or pathologic confirmation.

Probable stent thrombosis is considered to have occurred after intracoronary stenting in the

following cases:

1) Any unexplained death within the first 30 days.

2) Irrespective of the time after the index procedure any MI, which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

Possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of trial follow-up.

Bleeding was defined according to the Bleeding Academic Research Consortium (BARC)

Type 0 : no bleeding

Type 1 : bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional ; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2 : any overt, actionable sign of hemorrhage (eg. More bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4 or 5 but does meet at least one of the following criteria : (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation.

Type 3 :

Type 3a :

- overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is

related to bleed

- any transfusion with overt bleeding

Type 3b :

- overt bleeding plus hemoglobin drop ≥ 5 g/dl (provided hemoglobin drop is related to bleed)

- cardiac tamponade

- bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)

- bleeding requiring intravenous vasoactive agents

Type 3c :

- intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)

- subcategories confirmed by autopsy or imaging or lumbar puncture

- intraocular bleed compromising vision

Type 4: CABG-related bleeding

- perioperative intracranial bleeding within 48 h

- reoperation after closure of sternotomy for the purpose of controlling bleeding

- transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†

- chest tube output ≥2L within a 24-h period

Type 5: fatal bleeding

Type 5a: probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b: definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Clinically-driven target lesion revascularization (TLR) was defined as PCI or surgery for either an operator-defined restenosis in the treated lesion together with angina symptom and/or documented ischemia or for a > 70% core-laboratory defined restenosis when neither symptoms or ischemia were present.

Urgent TLR was defined as TLR done within 48 hours after hospital admission for symptomatic in-stent restenosis or stent thrombosis associated with new resting ECG changes and/or a rise of biomarkers (CK/MB or troponin).

Device success was defined as the successful delivery and deployment of a study stent to the target lesion with an estimated <20% residual stenosis and either a TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure using study stents only.

Lesion success was defined as the successful delivery and deployment of a study stent to the target lesion with an estimated <20% residual stenosis and either a TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure using any percutaneous method and/or non-study stents.

Procedure success was the successful treatment of all target lesions without the occurrence of death, MI, or target vessel repeat revascularization during the hospital stay.

E: <u>Methods for time-updated Cox proportional hazards models</u>

To model the effect of major bleeding or thrombotic events on subsequent death, we used Cox proportional hazards models with a time updated covariate, a well-established statistical methodology (see for example "Andersen, Encylopedia of Biostatistics,2005, Chapter: Time-Dependent covariates"). This is achieved by splitting records for an individual into relevant segments of follow up and then running a proportional hazards model on the modified data. For example, suppose who has a bleeding event after 69 days and subsequently dies after 300 days. Their original record is:

Subject ID	Death	Start of Follow up	End of follow up	Time to major bleeding
1	1	0	300	69

To fit a model with a time-varying covariate the data is modified to:

Subject ID	Death	Start of Follow up	End of follow up	Time to major bleeding	After major bleeding
1	0	0	69	69	0
1	1	69	300	69	1

The covariate in the "after switch" column can now be used to compare the rate of death before and after major bleeding events. Splitting follow up into time periods (0-7, 8-30, >30 days) after the event is a natural extension of this methodology. From a technical standpoint the new hazard function becomes:

$$h_{0i}(t) = \exp(\propto (t) + \beta_1 x_{i1} + \beta_2 x_{i2}(t))$$

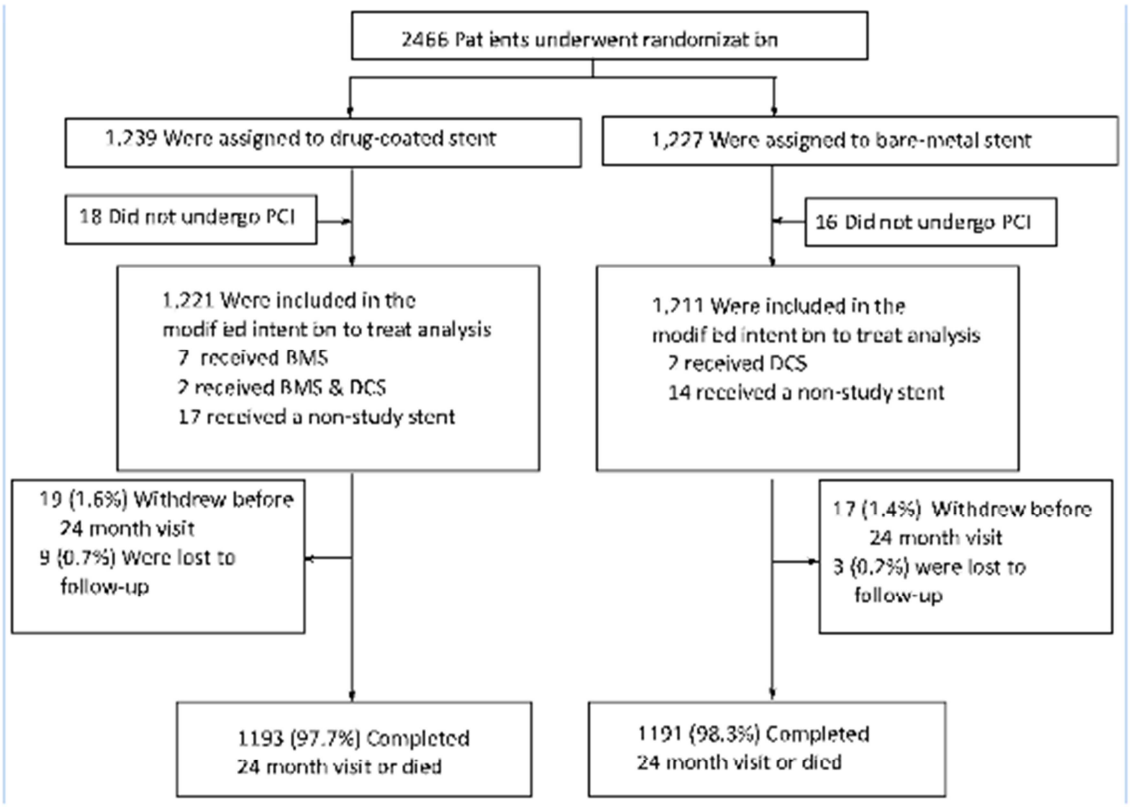
where $\propto (t)$ is the baseline hazard function, x_{i1}represents a "normal" (ie one that does not change over time), and $x_{i2}(t)$ represents a covariate that is allowed to vary over time. β_2 then represents the log hazard ratio per unit change in the time-dependent covariate.

F: Supplementary Tables and Figures

Table S1. Covariates assessed for inclusion in prediction models for major bleedings and thrombotic events

Patient characteristics	Procedural characteristics
Age	Type of trial stent
Gender	SVG target lesion (1 or more)
BMI	Bifurcation target lesion (1 or more)
Hypertension	Total stent length
Hypotension (≤100 mmHg at baseline)	Maximum stent diameter
Measured systolic BP at baseline (continuous)	Overlapping stents implanted
Active smoker	Number of stents implanted
Congestive heart failure	Multivessel procedure
Peripheral arterial disease	Residual stenosis reported > 50% or final TIMI flow < 3
Prior CABG or PCI	GP IIb-IIIa blockers used during procedure
Prior MI	
Prior stroke	
Planned use of OAC post-PCI	
Non-skin cancer < 3 years	
Creatinine clearance < 40 ml/min	
Plasma creatinine	
Hemoglobin < 11 g/dl or recent TF or admission for bleeding < 1 year	
Hemoglobin	
Surgery planned < 1 year	
Diabetes	
ACS presentation (NSTEMI or STEMI)	
Multivessel disease	

Figure S2: Study group assignment and follow-up



PCI denotes percutaneous coronary intervention, BMS, Bare-metal stent, DCS, Drug-coated stent.

Note: the 24 month follow-up contact was scheduled to take place after 24 months $\pm$ 60 days. Because a significant proportion of patients were contacted during the earlier part of that time-window, the number of patients at risk at 730 days is reduced in Figure 1 A and B.

Table S3 Baseline Patient Characteristics and Inclusion Criteria

	DCS, N (%) (n=1,221)	BMS, N (%) (n=1,211)
Mean age	75.7±9.4	75.7±9.3
Female gender	364 (29.8)	374 (30.9)
Mean BMI	27.5±4.8	27.2±4.6
Diabetes	414 (34.0)	391 (32.3)
Hypertension	952 (78.1)	961 (79.6)
Hypercholesterolemia	742 (62.0)	746 (62.7)
STEMI	57 (4.7)	48 (4.0)
NSTEMI	273 (22.4)	281 (23.2)
Unstable angina	177 (14.5)	193 (15.9)
Stable CAD	714 (58.5)	689 (56.9)
Multi vessel disease	755 (62.9)	738 (61.6)
Prior myocardial infarction	237 (19.6)	258 (21.4)
Previous PCI	270 (22.2)	265 (21.9)
Previous CABG	115 (9.4)	122 (10.1)
Congestive heart failure	175 (14.4)	150 (12.4)
Atrial Fibrillation	424 (34.9)	418 (34.6)
Previous stroke	132 (10.9%)	110 (9.1%)
Peripheral vascular disease	190 (15.7)	190 (15.8)
Chronic obstructive lung disease	131 (10.9)	141 (11.7)
CRUSADE score	34.1 $\pm$ 0.4	34.6 $\pm$ 0.4
Inclusion criteria[+]		
Age >=75	788 (64.5)	776 (64.1)
Planned continued OAC	448 (36.7)	431 (35.6)
Hemoglobin < 11g/l or transfusion <=30 days	185 (15.2)	194 (16.0)
Platelets < 100,000/m3	20 (1.6)	18 (1.5)
Admission for bleeding in last year	46 (3.8)	33 (2.7)
Stroke in last year	15 (1.2)	24 (2.0)
Previous intra-cerebral hemorrhage	14 (1.1)	19 (1.6)
Severe Chronic Liver Disease	11 (0.9)	10 (0.8)
Creatinine clearance <40 ml/min	219 (17.9)	245 (20.2)
Cancer in last 3 years*	119 (9.7)	120 (9.9)
Planned major surgery in following year	187 (15.3)	211 (17.4)
Steroids / NSAID planned >30 days post PCI	38 (3.1)	34 (2.8)
Expected noncompliance for >30 days DAPT	41 (3.4)	47 (3.9)

None of the baseline characteristics differ at $p<0.05$

+ not mutually exclusive

* excludes skin cancer

^Mean ± standard deviation

BMS: bare metal stent; BMI: body mass index; CABG: coronary artery bypass grafting; CAD: coronary artery disease; DAPT: dual antiplatelet therapy; DCS: drug coated stent; NSAID: non-steroid anti-inflammatory drug; NSTEMI: non-ST elevation myocardial infarction; OAC: oral anticoagulation; PCI: percutaneous coronary intervention; STEMI: ST elevation myocardial infarction

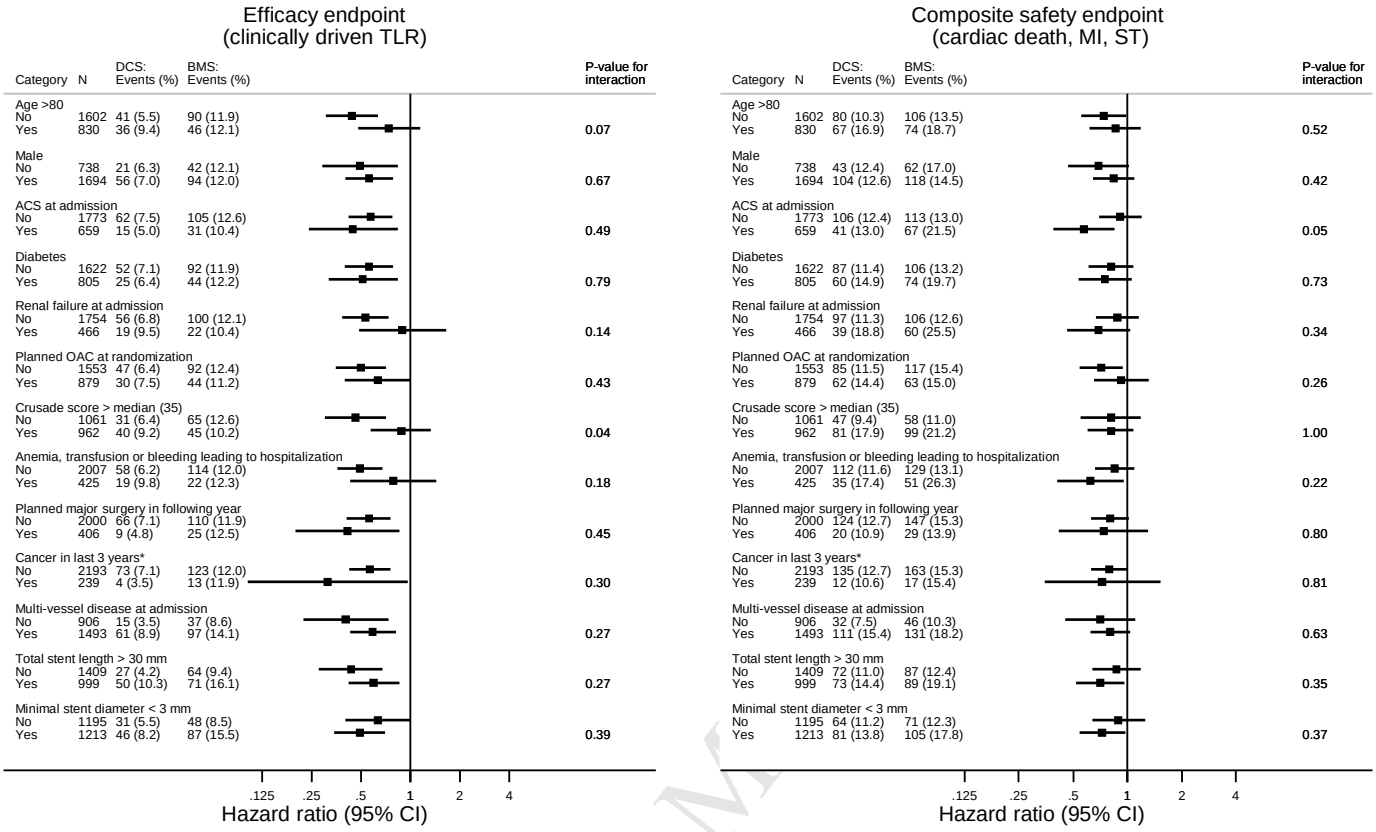
Table S4: antithrombotic medication during follow-up

Medication	DCS n (%)	BMS n (%)	p-value
At discharge			
DAPT at discharge	1176 (96.6)	1172 (96.9)	0.52
Aspirin + Clopidogrel	1099(90.0)	1101(90.9)	0.44
Aspirin + Prasugrel	13 (1.1)	16 (1.3)	0.56
Aspirin + Ticagrelor	63 (5.2)	54 (4.5)	0.42
Aspirin + Ticlopidine	1 (0.1)	1 (0.1)	1.00
OAC at discharge	443 (36.3)	418 (34.6)	0.36
AVK	394 (32.3)	382 (31.6)	0.70
Other OAC	49 (4.0)	36 (3.0)	0.18
Triple therapy (OAC + DAPT)	408 (33.5)	387 (32.0)	0.44
AVK + Clopidogrel alone	32 (2.6)	30 (2.5)	0.82
1 month			
DAPT at start of 1 month follow up window*	1146 (95.3)	1135 (95.0)	0.85
DAPT at end of 1 month follow up window*	110 (9.2)	116 (9.7)	0.65
No APT	15 (1.3)	12 (1.0)	0.58
OAC	410 (34.6)	387 (33.0)	0.43
12 month			
DAPT	85 (7.7)	106 (9.7)	0.10
SAPT	928 (83.8)	903 (82.9)	0.54
Aspirin	802 (85.7)	778 (85.8)	0.95
Clopidogrel	124 (13.7)	127 (13.6)	0.95
Ticagrelor	4 (0.4)	3 (0.3)	0.73
Prasugrel	3 (0.3)	2 (0.2)	0.68
Ticlopidine	0 (0.0)	0 (0.0)	NA
No APT	95 (8.6)	80 (7.3)	0.35
OAC	416 (37.5)	405 (37.2)	0.66
24 month			
DAPT	55 (5.3)	78 (7.6)	0.03
SAPT	816 (78.8)	784 (76.8)	0.26
Aspirin	731 (89.5)	692 (88.3)	0.40
Clopidogrel	82 (10.5)	87 (11.1)	0.49
Ticagrelor	0 (0)	4 (0.5)	0.06
Prasugrel	3 (0.4)	1 (0.1)	0.67
Ticlopidine	0 (0.0)	0 (0.0)	NA
No APT	164 (15.8)	159 (15.6)	0.87
OAC	390 (37.7)	388 (38.0)	0.88

APT: antiplatelet therapy; AVK: anti-vitamin K; DAPT: dual antiplatelet therapy; OAC: oral anticoagulant; SAPT: single antiplatelet therapy

- One month follow up window from 23 to 37 days

Supplementary Figure S5: Subgroup analyses for the primary safety and primary efficacy endpoints at 2-year follow-up



Scores on the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines) bleeding risk scale (range from 1 to 100, with higher scores indicating a higher risk of major bleeding). The median score of 35 in our trial was chosen as the cutoff value. Cancer excluded skin cancer. ACS denotes acute coronary syndrome, and OAC oral anticoagulation.